REMARKS

Claims 42-67 are pending for examination. Claims 42 and 56-60 have been amended. Claims 54 and 55 have been canceled and new claims 68-78 have been added. Claims 42 and 71 are independent claims. No new matter has been added.

Support for the amendments to claim 42 are found on page 8 lines 10-11 (nucleic acids containing unmethylated CpG dinucleotides), original claim 12 and page 19 lines 12-31 (modified backbone, including phosphorothioate backbone modification), and page 20 lines 6-7 (human subject). Support for a length limitation of 8-100 nucleotides is found in parent patent applications which are incorporated by reference, including at least US 08/276,358 on page 5 lines 33-35 (preferred oligonucleotides are in the range of 2-100 base pairs) and page 8 lines 23-25 (of those tested ODNs shorter than 8 nucleotides were non-stimulatory). Claims 57-59 were amended to be consistent with amended claim 42. Claims 56 and 60 were amended to reduce the scope of the claim.

Support for new claims 68, 72 and 73 directed to the administration of a chemotherapy or immunotherapy is found in the specification at least on page 54 lines 20-25. Support for new claims 69 and 78 directed to the administration by a subcutaneous route is found in the specification at least on page 55 lines 25-27. Support for new claim 73 directed to a phosphorothioate modification is found in the specification at least in original claim 13 and page 19 lines 12-31. Support for new claim 75 directed to a length limitation of 8-40 nucleotides is found in parent patent applications which are incorporated by reference, including at least US 08/276,358 on page 5 lines 33-35. Support for new claim 76 directed to at least 2 CpG motifs is found in the specification at least on page 21 lines 16-18 (the magnitude of stimulation typically could be increased by adding more CpG dinucleotides). Support for new claim 77 wherein the CpG is not palindromic is found in the specification at least on page 22 lines 17-19 ("For nucleic acids longer than 8 base pairs, non-palindromic motifs containing an unmethylated CpG were found to be more immunostimulatory"). Support for new claim 71 directed to a method of treating non small cell lung carcinoma is found in the specification at least on page 14 lines 11-15.

Rejections under 35 U.S.C. §112

Claims 42-58, 66 and 67 have been rejected under 35 U.S.C. §112 for failing to comply with the written description requirement. According to the Examiner, the "specification indicates one sub-genus of CpG containing oligonucleotides, which comprise an unmethylated CpG motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3', thus indicating distinct structural and functional properties of one sub-genus of molecules embraced by the claims." (Office Action page 3).

It is clear from the language of the claims and the specification that Applicants had possession of the invention at the time the application was filed. The specification includes a description of a class of oligonucleotides that are useful for treating cancer. This class of oligonucleotides includes an unmethylated CpG dinucleotide. The specification also describes some embodiments of that class of oligonucleotides, some of which are preferred embodiments. These include, for instance, a phosphate backbone modification, such as a phosphorothioate modification, length limitations, i.e. 8-40 or 8-100 nucleotides, multiple CpG dinucleotides, and specific ODN formulas.

Applicants have amended claim 42 to recite additional structure and to clarify that the claimed CpG dinucleotide is unmethylated. Amended claim 42 includes the limitation that the CpG oligonucleotide include at least one unmethylated CpG dinucleotide and that the oligonucleotide has a phosphate backbone modification and a length of 8- 100 nucleotides. Each of these features further structurally defines the class of oligonucleotides. It is believed that such structural limitations are sufficient to adequately describe the claimed class of CpG oligonucleotides. One of skill in the art can recognize the identity of the claimed subject matter from the plain language of the claim. Additionally, such language is clearly set forth and defined in the specification.

Enzo Biochem, Inc. v. Gen-Probe Inc, ("Enzo") was cited in the Office Action in support of the rejection for lack of adequate structure in the claims. The facts of the Enzo case, however, are distinguishable from the facts of the instant application.

The Examiner points to an example provided by the Enzo court for the purpose of demonstrating a lack of written description. The example presented by the Enzo court related to language referring to a Steroid having the ability to reduce inflammation. The court concluded that such functional language in the absence of any structure does not distinguish the claimed steroids from other steroids having that same function. The facts of the example described by the Enzo court are different from the present case. In the present case, the claim elements at issue are a well defined set of oligonucleotides, described by structure, and not solely by function. In the section of Enzo referred to by the Examiner the court concludes by stating that a "mere idea or function is insufficient for written description" and that a "description of what a material does, rather than what it is, usually does not suffice." (citing *University of California v. Eli Lilly* (Office Action at page 4.) The class of CpG oligonucleotides of the instant invention is not claimed by its function or "what it does", but rather it is claimed using structural elements. Each of the structural elements is described in the specification. One of skill in the art reading the claims would understand which oligonucleotides fall within the claims.

The Examiner has cited *Fiddes v. Baird* ("Fiddes", 30 USPQ2d 1481 at 1483) for the argument that "one cannot describe what one has not conceived." The facts of Fiddes are distinguishable from the facts of the instant case. In Fiddes the issue decided by the court was whether a specification lacking the specific naturally occurring gene sequence of a mammalian FGF was sufficient to provide written description of a broad claim to a DNA encoding mammalian FGF. The court found that it was not because the specification and claim included no structure to describe the molecule. In the present case applicants have defined the class of molecules using structure in the claim. Further, applicants have provided multiple examples of species that fall within this class of oligonucleotides. Applicants have conceived of this well defined set of oligonucleotides and have described them structurally.

Accordingly, Applicant's specification provides an adequate written description of claims 42-58, 66 and 67 as presently amended. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph therefore is requested.

Rejections under 35 U.S.C. §112

Claims 42-67 have been rejected under 35 U.S.C. §112 for a lack of enablement. According to the Examiner, the specification does not provide adequate guidance on the administration of the CpG oligonucleotides for the treatment of cancer. The examiner has considered the factors set forth in *Ex parte Forman* ("Forman", 230 USPQ 546 (BPAI 1986)). Applicants address each of these points in turn.

The nature of the invention:

The invention relates to methods of treating cancer using an immunostimulatory oligonucleotide containing an unmethylated CpG dinucleotide.

The breadth of the claims:

The Examiner has stated that the claims are very broad because they encompass any stabilized CpG-containing oligonucleotide and any chemotherapeutic and/or immunotherapeutic agent. As discussed above, the claims have been amended to add some additional limitations, such as a limitation on the length of the oligonucleotide and that the oligonucleotide has a phosphate backbone modification. The claims encompass a well defined class of molecules, CpG containing oligonucleotides, which Applicant has demonstrated produce an immune response consistent with the treatment of cancer.

Dependent claims 43 and 44 add the limitation that the CpG oligonucleotide is administered with a chemotherapeutic or immunotherapeutic agent. The key to the invention is the discovery that CpG oligonucleotides are useful for treating cancer. The inventors also recognized that CpG immunostimulatory oligonucleotides can be used with traditional anti-cancer agents to provide enhanced responses to the cancer. Such agents are well known in the art. There is no need for Applicant to provide detailed descriptions of known compounds.

The unpredictability of the art and the state of the prior art:

In support of the argument that the art is unpredictable, the Examiner has cited 2 publications (both of which were published after applicants priority date) to demonstrate that specific characteristics of the oligonucleotides are critical for their function. Agrawal et al was cited

by the examiner to demonstrate that the cytokine pattern produced by CpG oligoncueltides was dependent on the sequences flanking the CpG dinucleotide, the dose and route of administration and the host animal species.

The teachings of Agrawal et al do not demonstrate that the claimed invention was unpredictable at the time of the invention. Agrawal et al do not teach that all unmethylated CpG oligonucleotides don't work for stimulating an immune response. In fact, Agrawal et al, conclude on page 119 second column that "it is evident that CpG DNA is a powerful tool to modulate the immune system and can be exploited to treat a wide variety of diseases quite economically. Studies on the medicinal chemistry of CpG DNA have just begun and the preliminary results indicate several possible ways of further fine-tuning the immunomodulatory affects of first-generation CpG DNA by introducing site-specific chemical modifications." (emphasis added). The discussion of optimal properties by Agrawal et al does not suggest that the full scope of the claimed invention would not work. Agrawal et al actually describe the general properties that are associated with the claimed class of CpG oligoncueltides. For instance, it is taught that "In vitro, bacterial and synthetic CpG DNA have mitogenic effects on B cells [7], activate macrophages, dendritic cells (DCs) and monocytes to produce cytokines [8,9], and stimulate NK-cell lytic activity [6]. In vivo, these motifs induce splenomegaly [10, 11] (enlargement of the spleen) accompanied by proliferation of splenic B cells, increased expression of major histocompatibility complex (MHC) class II on B cells, increased synthesis of RNA and DNA, and an increased number of immunoglobulin-producing cells." (page 1114 first column, second paragraph). Following this general statement Agrawal et al, summarize findings arising from several years worth of research directed at optimizing the compounds. These discussions do not demonstrate the unpredictability of the class of CpG oligonucleotides.

Applicants have established in the specification that oligonucleotides having an unmethylated CpG dinucleotide provoke an immune response that is consistent with the treatment of cancer and other diseases. In the specification, Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered. This class of

oligonucleotides is described throughout the specification and their ability to produce an immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 – page 54, line 5) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has a characteristic pattern of cytokine expression. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG containing oligonucleotides.

It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on page 35 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. It is further taught that "Teleologically, it appears likely that lymphocyte activation by the CpG motif represents an immune defense mechanism that can thereby distinguish bacterial from host DNA."

Based on these teachings one of ordinary skill in the art would have expected, at the time of the invention, that CpG oligonucleotides would possess the stated immune stimulatory effects. The claimed invention was not unpredictable.

Additionally, the data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 1984 (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not

a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims.

According to the MPEP section 2164.05 (a) "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered" In the instant circumstance the post-filing date reference (Agrawal et al) does not provide "evidence of what one skilled in the art would have known on or before the effective filing date of the patent application" or "state that a particular invention is not possible years after the filing date". Instead it describes years worth of post-filing date studies that have focused on optimization techniques and developing optimized products.

Crooke et al., has been cited to demonstrate that phosphorothioate oligonucleotides "have significant limits" and because they may have potential toxicity issues. 4 reasons were provided for demonstrating the limits of phosphorothioates: 1) they have relatively low affinity per nucleotide unit, 2) they do not cross the blood brain barrier, 3) they are not significantly orally bioavailable and 4) they may display dose-dependent pharmacokinetics. These reasons do not demonstrate the unpredictability of using a phosphorothioate CpG oligonucleotide in the methods of the invention. For instance, the fact that phosphorothioate oligonucleotides have low affinity per nucleotide unit is relevant to the antisense mechanism. CpG oligonucleotides are not functioning through an antisense mechanism of action. The fact that they do not cross the blood brain barrier and don't have significant oral bioavailability is not essential to the invention. Many cancer treatments are administered to a patient in a hospital by systemic modes of administration or direct application to a tumor site. The fact that they may display dose-dependent pharmacokinetics is not relevant because

such pharmacokinetic properties are common in the field. One of skill in the art simply needs to identify an appropriate dosage.

This issue of potential toxicities also does not support a determination that the claimed invention is unpredictable. In spite of Crooke's discussion of potential toxicities associated with oligonucleotides, Crooke teaches that several human clinical trials using phosphorothioate oligonucleotides were being conducted. Thus, the potential toxicity was not sufficient to stop the administration of these compounds to humans.

Working Examples and Guidance in the specification

The Examiner had indicated that the application does not include any working examples indicating that any CpG oligonucleotide can be useful for treating cancer.

It is well established that it is not essential for a patent application to include a working example in order to satisfy the requirements of 35 U.S.C. 112 first paragraph. "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." MPEP section 2164.02.

However, the instant patent application is not prophetic. The specification includes *in vitro* data on mouse and human cells, as well as *in vivo* data. Tables 1-2 demonstrate that many different CpG oligonucleotides are capable of activating murine B cells and inducing cytokine expression in murine cells *in vitro*. Table 5 depicts an experiment in which multiple CpG containing oligonucleotides were tested for their ability to induce cytokine expression in human cells. The experiment of Table 5 demonstrated that multiple CpG oligonucleotides were capable of inducing cytokine expression and notably an IL-12 response. Studies including the one described in Example 4 and Table 3 identified the ability of CpG oligonucleotides to induce NK cell activity. The data obtained in the *in vivo* experiments such as those shown in Table 4 appear to be consistent with the data obtained in the *in vitro* experiments, confirming that the pattern of cytokine release and Th1 effects could be exploited *in vivo*.

Several Phase I and II studies have been performed in humans to date. For instance, subcutaneous administration has been performed in humans for a cancer trial. The data are

described in Kim et al., Blood, volume 4, issue 11, abstract # 743, Nov. 16, 2004. Toxic effects that would halt further human trials were not observed, even though the patients were provided CpG oligonucleotides in very aggressive doses. The abstract concludes that "weekly doses up to 0.36 mg/kg have been well tolerated." Additionally improved responses to the CpG treatment were observed.

As described above, numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims.

Quantity of experimentation

The examiner concludes that undue experimentation would be required to practice the invention because one of skill in the art would be required to perform additional experimentation. The courts have established that additional experimentation can be performed while meeting the requirements of 35 U.S.C. 112. The court in Ex parte Forman et al (230 USPQ 546 at 547 (BPAI 1986)) held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." Thus, the fact that additional experimentation may be required is not sufficient to suggest that the claims are not enabled.

With respect to the claimed invention, Applicants have provided adequate description in the specification to enable one of skill in the art to practice the claimed invention with merely routine experimentation. The specification provides a description of a class of molecules (CpG containing oligonucleotides) (see for instance specification page 8 lines 10-30 and pages 15-20), a description of how to make such molecules (see for instance specification pages 52-53, other methods for making oligonucleotides are well known in the art), a description of the immune responses produced by such molecules (i.e. induction of IFN-gamma and NK cell activation, that are particularly useful in the treatment of cancer, see for instance data throughout the specification)), a teaching that such molecules are useful in the treatment of cancer (see for instance specification page 14 lines 11-15), a

description of modes of administration, including subcutaneous (see for instance specification page 55 lines 24-27), and a description of methods for determining effective amount (see for instance specification page 57). Based on these descriptions and what was known in the art at the time of the invention one of skill in the art could practice the methods of the invention using only routine experimentation. For instance, the attached abstract from Kim et al describes the subcutaneous administration of a CpG oligonucleotide to humans at several doses with 25% of the patients achieving clinical response including some patients with complete remission.

The Examiner has also stated that one "would have to show how a CpG-containing oligonucleotide could function as immunostimulatory molecules." Applicants have shown throughout the specification using actual working examples and numerous CpG oligonucleotides that these molecules stimulate an immune response.

The Examiner has concluded this section by stating that undue experimentation would be required because one of skill in the art would have to "show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonucleotides would not work for treating or preventing any cancer". The examiner has not made a prima facie case establishing that there are art-recognized problems that are necessary to overcome. Each of the references cited by the Examiner under the section related to unpredictability, do not demonstrate that at the time the patent application was filed that the claimed invention was unpredictable.

Level of skill in the art

Applicants agree that the level of skill in the art is high.

Conclusion:

The Examiner concludes that "the instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the claims. One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example. the instant application does not give

guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects." (Office Action page 10). Applicants disagree that this is the appropriate legal standard for the issue of whether a claim is enabled.

Firstly, in vivo data is not required in order to enable a claim. As discussed above, data is not an absolute requirement. Regardless the specification includes substantial data including in vitro and in vivo data related to demonstrating the ability of multiple CpG oligonucleotides to stimulate an immune response.

Additionally, applicant is not required to provide exact details for specific times or frequencies of administration or dosages. According to the MPEP section 2164.01(c) "For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. § 112, first paragraph." As stated in the Crooke reference, discussed above, phosphorothioate oligonucleotides were currently being used in clinical trials for other purposes (antisense studies). Thus modes of administration and bioavailability of these types of molecules had already been studied. Identifying exact doses for optimal immune stimulation is within routine experimentation of the skilled artisan. As discussed above, Applicants have provided descriptions in the specification of preferred dosage ranges and routes of administration.

Accordingly, Applicant's specification provides an adequate guidance such that claims 42-67 comply with the enablement requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph therefore is requested.

Rejections under Judicially Created Doctrine of Obviousness Type Double Patenting

Claims 42-65 have been rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-22 of US Patent No. 6,653,292.

Initially, Applicants wish to point out that the nature of the rejection is unclear. It is unclear whether the rejection is one of obviousness type double patenting, which can be overcome with a

terminal disclaimer, or a "same invention" type double patenting (35 USC 101), which cannot be overcome by a terminal disclaimer. The rejection is referred to as falling under the judicially created doctrine of obviousness type double patenting and it is stated at the introduction of the rejection that "the conflicting claims are not identical." However, the conclusion of the rejection states "thus, the claims 1-22 of U.S. Patent No. 6,653,292 (Krieg and Weiner) anticipate the instant claims." For this reason, Applicants address both grounds for double patenting.

A rejection of the claims under 35 USC 101 as the same invention type double patenting is not appropriate. The pending claims are not identical to the claims of the issued patent. According to the MPEP (804.02 II) "claims that differ from each other (aside from minor differences in language, punctuation, etc.), whether or not the difference is obvious, are not considered to be drawn to the same invention for double patenting purposes under 35 USC 101."

In response to the rejection under the judicially created doctrine of obviousness type double patenting, Applicants hereby file a terminal disclaimer. It is believed that the Terminal disclaimer should be sufficient to overcome the rejection.

Inventorship

It has recently come to applicants attention that two additional inventors have contributed to the claimed subject matter. Applicants enclose herewith paperwork to add the additional inventors.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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